IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
MacKay et al.	)	Group Art Unit: 1644
	)	
Serial No.: 10/045,574	)	Examiner: Haddad, Maher M.
	)	
Filed: November 7, 2001	)	
	)	
For: BAFF, INHIBITORS THEREOF AND THEIR USE IN THE MODULATION OF B-CELL RESPONSE AND TREATMENT OF AUTOIMMUNE DISORDERS	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION OF LESLIE A. MCDONELL

Pursuant to *In Re* Hawkins 179 U.S.P.Q. 157 (C.C.P.A. 1973), I, Leslie A. McDonell declare:

The specification of U.S. Application Serial No. 10/045,574 has been amended, in part, to recite SEQ ID NO:27 and SEQ ID NO:28 and references to the respective accession numbers. The sequences set forth under SEQ ID NO:27 and SEQ ID NO:28 and the accession numbers are the same as disclosed in Figure 1 in Thompson et al. (2001) Science, 293:2108, previously incorporated by reference at page 17, lines 5-6, of the specification.

I further declare that all statements made herein of my own knowledge are true; that all statements made on information and belief are believed to be true; that

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these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

December 31, 2003
Date

Leslie A. McDonell
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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION OF SUSAN KALLED UNDER 37 C.F.R. § 1.132

I, Susan Kalled, declare:

1. I am an inventor of the subject matter in application Serial No. 10/045,574.

2. I am a Principal Scientist in Molecular and Cellular Biology at Biogen Idec and have been employed at Biogen Idec (and its predecessor company, Biogen) in various scientific capacities since 1995. I received my Ph.D. in Immunology from Tufts University in 1991, and my B.A. in Microbiology from the University of New Hampshire in 1983. Most recently, I have been the Project Leader at Biogen Idec for the BAFF

Program, and have authored or co-authored four review articles on the subject of BAFF and other TNF family members.

3. I have read and understood application Serial No. 10/045,574, including the claims as amended in the response filed with this Declaration. The claims, as amended, are drawn to methods of treating a patient having Sjögren's syndrome, whereby a soluble BAFF-R is administered in an amount and for a period of time sufficient to reduce immunoglobulin production and/or B-cell growth.

4. We have evaluated treatment of BAFF transgenic (BAFF Tg) mice with a soluble form of a BAFF receptor, BCMA (B cell maturation antigen).

5. BAFF Tg mice expressing full-length murine BAFF under the control of liver specific regulatory sequences were generated as described in Mackay et al. (1999) *J. Exp. Med.*, 190(11):1697-710. BCMA-Fc was prepared as described in Thompson et al. (2000) *J. Exp. Med.*, 192(1):129-35.

6. Six-month-old BAFF Tg mice and non-Tg littermate controls received intraperitoneal injections of PBS, 400 µg of BCMA-Fc, or 400 µg of polyclonal human IgG (hIg) once a week for five weeks.

7. We monitored proteinuria each week to assess renal function, and upon sacrifice, analyzed spleen weight and total serum Ig titers. The effect on splenomegaly was determined by examining spleen weights of treated and control mice. Splenomegaly and hypergammaglobulinemia were reduced upon treatment with BCMA-Fc as compared to a control. As shown in Table 1, the geometric mean of total serum Ig was reduced four-fold in BAFF Tg mice treated with BCMA-Fc, a significant

reduction (p=0.02) when compared with BAFF Tg mice treated with control antibody. These results indicate that immunoglobulin production is inhibited following administration of the soluble BAFF receptor.

Table 1.

Mouse/Treatment		Total Serum Ig (mg/ml)
BAFF Tg/hIgG		
802C06		6.7
816B82		4.7
816D20		10.5
816E34		4.4
823C48		13
823C69		9.7
	Geo Mean	7.5
BAFF Tg/BCMA-Fc		
802C05		2
802C07		0.7
802C09		1.4
823C39		2.2
823C41		1.5
823C45		8
	Geo Mean	1.9
Non-Tg/hIgG		
823B64		3.9
823B66		2.5
823B94		5.6
823B98		2.8
	Geo Mean	3.5

8. W furth r assessed the effect of BCMA-Fc on the development of nephritis in the BAFF Tg mice. Proteinuria scores were determined prior to, during and after treatment. At the end of the 5-week treatment period, hIgG-treated mice showed no significant improvement over the pre-treatment score when compared to PBS-treated controls. In contrast, BCMA-Fc treated mice exhibited an average 50% improvement in proteinuria score at the end of the 5-week treatment period (Fig. 1). These results further demonstrate that immunoglobulin production is inhibited following administration of a soluble BAFF receptor.

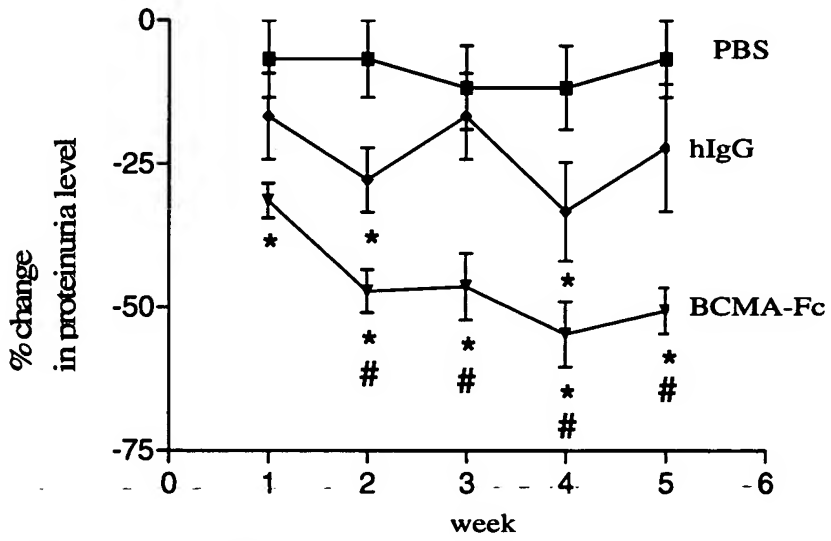
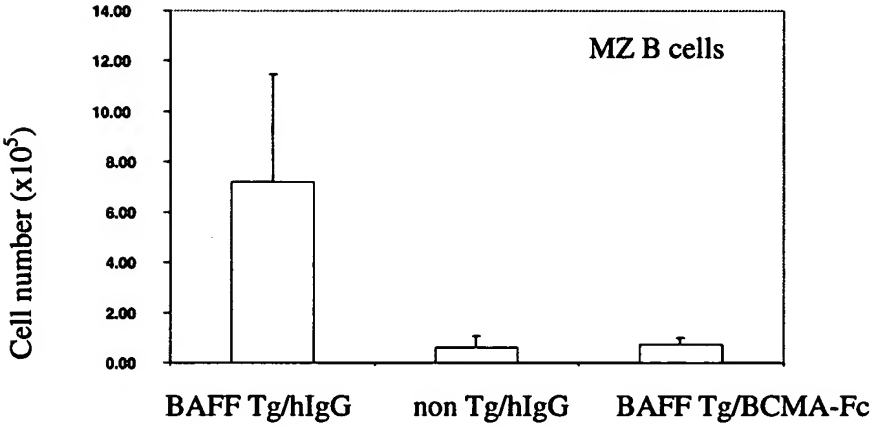


Figure 1

9. We also assessed the effect of BCMA-Fc on B cell numbers in the BAFF Tg mice. Single cell suspensions from spleens were prepared and analyzed by flow cytometry as described in Mackay et al. (1999) *J. Exp. Med.*, 190(11):1697-710. Splenocytes were stained with a fluorochrome-conjugated anti-B220 mAb to detect B lymphocytes as described in Thompson et al. (2001) Science, 293:2108-2111.

10. BAFF Tg mice treated with control antibody (BAFF Tg/hIgG) had elevated numbers of B lymphocytes, including marginal zone (MZ, IgM^{bright}/ IgD^{-}/ $CD21^{bright}$) (Fig. 2, upper panel) and mature (IgM^{low}/ IgD^{+}/ $CD21^{int}$) (Fig. 2, lower panel) B cells. Following treatment with BCMA-Fc (Tg BCMA), splenic levels of MZ B cells were reduced 10-fold (Fig. 2, upper panel) and mature B cells were reduced 11-fold (Fig. 2, lower panel) compared to BAFF Tg mice treated with control antibody (Tg hIgG). These results indicate that B cell growth is inhibited following administration of a soluble BAFF receptor.


MZ B cells
Cell number (x10^5)
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
BAFF Tg/hIgG
non Tg/hIgG
BAFF Tg/BCMA-Fc

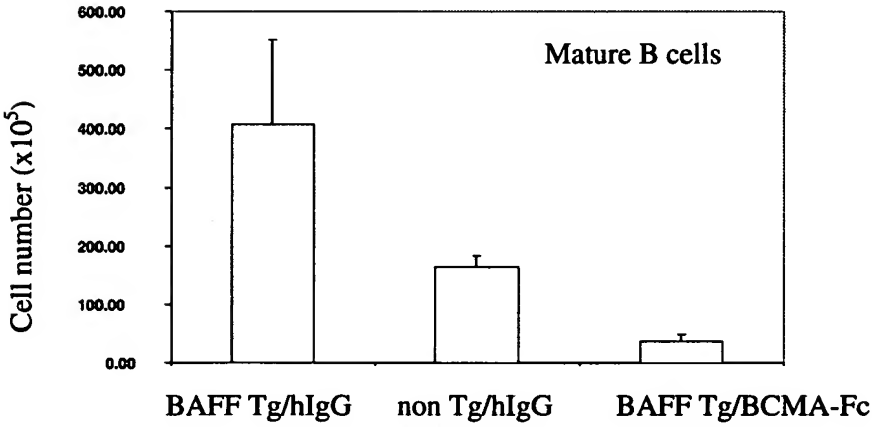

Mature B cells
Cell number (x10^5)
600.00
500.00
400.00
300.00
200.00
100.00
0.00
BAFF Tg/hIgG
non Tg/hIgG
BAFF Tg/BCMA-Fc

Figure 2

11. The above results demonstrate that sequestration of BAFF in a mouse model of Sjögren's syndrome leads to a reduction in total serum Ig, splenolomegaly, and the numbers of MZ and mature B cells.

12. Based on these results, I expect that administration of soluble forms of other BAFF receptors, such as BAFF-R and TACI, as well as anti-BAFF antibodies, will likewise result in a reduction in total serum Ig, splenolomegaly, and the numbers of MZ and mature B cells.

13. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: Dec 23, 2003 By: Susan Kalled
Susan Kalled, Ph.D.